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Organic Compounds

The present invention relates to pharmaceutical compositions comprising 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (also referred to herein as licarbazepine) or the pure enantiomers of licarbazepine, all together hereinafter referred to as "the compounds of the invention".

Licarbazepine (also known as MHD) is well known from the literature [see for example Schuetz H. et al., Xenobiotica (GB), 16(8), 769-778 (1986)] and can be prepared synthetically starting from oxcarbazepine according to conventional methods, e.g. as described in US 3,637,661. Licarbazepine is indicated to be suitable for the treatment of psychosomatic disturbances, epilepsy, trigeminal neuralgia and cerebral spasticity. It was demonstrated that the racemate of licarbazepine and both of its pure enantiomers are of equal efficacy against epilepsy.

The term "licarbazepine" as used herein refers to the racemic mixture of (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide and (R)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. In the present invention licarbazepine, mixtures of (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide and (R)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide comprising one of both enantiomers in excess as well as the pure enantiomers of licarbazepine can be employed

The pure enantiomers of licarbazepine can be obtained starting from the racemate by procedures known as such. For instance, the racemate may be separated into its enantiomers through the formation of diastereomers, e.g. as disclosed in WO02/092572, or, alternatively, by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands. In one embodiment of the invention, the pure enantiomers of licarbazepine are prepared by an enantioselective process according to the procedures described in the Examples below.

The mechanisms by which the compounds of the invention exert their anticonvulsant effects are not completely understood, but may be partly due to effects on ion flow across neuronal

membranes. Pharmacokinetics and absorption sites and mechanisms of the compounds of the invention are not understood in detail however.

Licarbazepine is slightly soluble in water (3.2 mg/ml at 25°C). In view of this physical property of licarbazepine, a parenteral formulation of the compound can be prepared as described in EP 1033988. Despite the merits of the known parenteral dosage form, there remains a need to establish an oral dosage form of the compounds of the invention. One of the problems that may occur is the fluctuation of blood levels of the compounds of the invention on repeated administration which may be associated with side effects.

After exhaustive testing surprisingly we have now found pharmaceutical oral controlled release compositions with advantageous properties, which are capable of being administered once a day and which are particularly well tolerated and have a good bioavailability in a wide variety of patient populations.

Hence, the invention provides in one aspect pharmaceutical oral controlled release compositions comprising at least one of the compounds of the invention adapted to be administered once a day (hereinafter "oral dosage forms of the invention"), in particular having a low fluctuation index for a better tolerability and a continuous symptom control with adequate Cmin values. Furthermore, the new pharmaceutical oral controlled release compositions have the advantage of a high AUC and a low Cmax.

Oral dosage forms of the invention may represent a considerable advantage over other oral dosage forms in that they are more convenient and/or safer for patients to use and increase the patient's compliance to therapy. The patient has to take the oral dosage form of the invention only once a day.

The term "once a day" as used herein means once every 20 to 28 hours, in particular once every 24 hours.

Preferred oral dosage forms of the invention have the form of a disintegrating tablet with modified release granules comprising licarbazepine. In such oral dosage forms, licarbazepine can be present in the granules in a ratio of 60 to 90 %, preferably 75 to 85 %, e.g. about 80 %, by weight of the modified release granules.

Preferably, the modified release granules comprise as retarding agents at least one polymer selected from polymethacrylates and ethycellulose. In one preferred embodiment of the invention, the oral dosage form comprises at least one polymethacrylate and ethycellulose.

Polymethacrylates can be present in the granules in a ratio of 5 to 25 %, preferably 10 to 20 %, e.g. about 15 %, by weight of the modified release granules.

Ethylcellulose can be present in the granules in a ratio of 2 to 10 %, preferably 4 to 8 %, e.g. about 6 %, by weight of the modified release granules.

Licarbazepine is preferably present in a ratio of 50 to 80 %, preferably from 60 to about 70 %, e.g. about 65 %, by weight of the total composition.

Polymethacrylates and ethylcellulose commonly used in tablet formulations may be used and reference is made to the extensive literature on suitable polymethacrylates and ethylcellulose, see in particular Fiedler's "Lexicon der Hilfstoffe", 4th Edition, ECV Aulendorf 1996 and "Handbook of Pharmaceutical Excipients" Wade and Weller Ed.(1994) which are incorporated herein by reference.

In a further aspect the present invention provides pharmaceutical oral controlled release compositions comprising licarbazepine wherein in use 70 to 90%, preferably 75 to 85%, of said licarbazepine is released in artificial stomach juices (e.g. 0,1 N HCl) within 6 hours indicated in standard in vitro dissolution tests at 37 degrees Celsius in water using sodium dodecyl sulphate as a solubilizing agent at a concentration of 1% for a 500 mg dosage form.

Clinical bioavailabilty trials, for instance, may be effected in conventional manner. For example, they may be effected over 7 or more days using a 500 mg dose of the compound of the invention. Conveniently at least 6, e.g 10, subjects are enrolled. In such studies the modified release characteristics, the bioavailability, the food effect, safety, tolerability, Cmax and AUC of the oral dosage forms of the invention can be determined.

The bioavailability of a drug substance depend on its physicochemical properties such as solubility and pharmacokinetic properties, e.g. site, rate and extent of absorption. Further, it

is known that food induces changes in the physiology of the gastrointestinal (GI) tract. These changes can result *i.a* in delays in gastric emptying, stimulation of bile flow and changes in pH. Food can also alter lumenal metabolism and physically or chemically interact with a drug substance. It is not surprising therefore that food can affect the bioavailability of a drug substance.

The effects of food are complicated and difficult to predict and will depend, for example on the nature of the meal, e.g. nutrient content, fluid volume, caloric content, and temperature. It follows that the presence of a food effect for a given drug substance can only be determined after exhaustive testing.

It is undesirable if the bioavailability of a drug substance differs depending upon whether a patient is in a fed or fasted state. This will at least be inconvenient to the patient who will have to time its medication relative to the taking of meals.

It is surprising therefore that it was discovered that an oral dosage form of licarbazepine may be administered to a patient without regard to the condition of the patient, i.e. whether the patient is in a fed or fasted state.

Accordingly, the invention provides in one of its aspects an oral dosage form of the invention having no food effect when administered to a patient.

Accordingly, in another aspect of the invention there is provided a package comprising an oral dosage form of the invention and instructions for use said instructions providing that the oral dosage form may be taken equally by patients who have eaten or who are in a fasted condition.

More particularly, the present invention provides an oral dosage form of the invention packaged in combination with written instructions which instructions provide that the dosage form may be taken equally with or without food.

The term “food effect” as used herein is intended to mean that the bioavailability of licarbazepine in the fed state differs from the bioavailability in the fasted state. The presence or absence of a food effect may be quantified by making Area Under the Curve (AUC)

and/or C_{max} measurements according to methods well known in the art. Typically AUC measurements and C_{max} measurements are made by taking timed biological fluid samples and plotting the serum concentration of licarbazepine against time. The values obtained represent a number of values taken from subjects across a patient population and are therefore expressed as mean values expressed over the entire patient population. By comparing the mean AUC and/or C_{max} values, one can determine whether licarbazepine exhibits a food effect.

A "fed" subject conveniently may be considered as a subject that has fasted for at least 10 hours before receiving a standard FDA recognised high fat meal. The licarbazepine may then be administered with water shortly after completion of the meal, e.g. within 5 minutes thereof. Preferably no food should be taken for a period of, e.g. 4 hours after receiving licarbazepine although small quantities of water may be permitted after, e.g. 2 hours after receiving the licarbazepine.

A "fasted" subject conveniently may receive licarbazepine with water after at least 10 hours fasting. Thereafter, no food may be taken for a period of, e.g. 4 hours although small quantities of water may be taken after, e.g. 2 hours after receiving licarbazepine.

A standard FDA high fat meal as referred to hereinabove may comprise any meal that would be expected to provide maximal perturbation due to the presence of food in the GI tract. Said high fat meal typically may comprise 50% of its caloric value in fat. A representative example may be 2 eggs fried in butter, 2 strips of bacon, 2 slices toast with butter, 4 ounces fried potato, and 8 ounces milk.

To study the effect of food on the bioavailability of licarbazepine formulations one may use any conventional study design known in the art, for example a randomised, balanced single-dose, two-treatment, two-period, two-sequence crossover design. Analysis may be carried out using, e.g. SAS PROC GLM, software from the SAS institute, Cary North Carolina.

A suitable study design to determine the bioavailability including the food effect would be a randomized, open-label, single oral dose, cross-over study wherein one can compare the bioavailability of the dosage form of the invention comprising a compound of the invention to a solution of the same compound of the invention, optionally also including oxcarbazepine

film coated tablets, and evaluate the food effect in healthy male subjects being in a fed or fasted condition.

In a study wherein the active ingredient is, for instance, licarbazepine, the oxcarbazepine film coated tablet (600 mg) and the dosage form of the invention comprising, 500 mg of licarbazepine can be administered together with 240 mL of tap water to the subjects. The licarbazepine clinical service form (500 mg) delivered as powder has to be solubilized first in 220 mL tap water prior to its administration. During the treatment periods that requires fasted conditions, the single dose of the study drugs is administered after an overnight fast of at least 10 hours. During the treatment period that requires fed conditions, each subject is requested to eat a FDA standardized high fat breakfast within 30 minutes prior to drug administration. No breakfast is served prior to drug administration during the treatment periods that requires fasting conditions and subjects have to continue to fast until 4 hours postdose. Safety and tolerability include continuous monitoring of adverse events, physical examinations, blood pressure and pulse rate measurement, ECGs recording, and routine laboratory tests (blood chemistry, urinalysis and hematology).

Accordingly, in one aspect the present invention provides a method of reducing intra-subject variability of bioavailability levels of licarbazepine for patients during oral licarbazepine therapy, said method comprising orally administering an oral dosage form comprising licarbazepine which shows no food effect when administered to a patient indiscriminately in the fed or fasted state, e.g. at any hour.

In a further aspect the present invention provides the use of licarbazepine for the preparation of a medicament for the treatment of patients with affective disorders.

The term “affective disorders” as used herein includes, but is not limited to uni- and bipolar depression, bipolar disorder, pre-menstrual dysphoric disorder, post-partum depression, post-menopausal depression, neurodegeneration-related depressive symptoms and depression occurring following cessation of psychostimulant intake, psychotic states, e.g. mania, schizophrenia, and excessive mood swings where behavioural stabilization is desired.

During a first 7 day period, subjects will be given one of the oral dosage forms of the invention under fasted conditions and during the second period subjects will be given the same treatment under fed conditions. Subjects will fast overnight for a minimum of 10 hours on the evening prior to the first dosing of a compound of the invention (period 1). Following dosing at e.g breakfast time, pharmacokinetic blood samples may be drawn and used for assays at adequate time intervals (e.g 0.5, 1, 2, 3, 4, 6, 8, 10,12,14,16, 18, 20, 22,24, 32 and 48 hours after administration).

The utility of the oral dosage forms of the invention for the treatment of affective disorders may be observed in standard animal tests and in standard clinical tests in, for example, clinical studies in bipolar disorders patients, for example, using dosages of licarbazepine in the range of an amount between about 500 and about 3000 mg per day, and in standard animal models.

The absorption profile of the compound of the invention may be quantified by making Area Under the Curve (AUC) measurements on single doses or at steady state.

Constant plasma levels of the compound of the invention indicate that the plasma levels of the compound of the invention show low fluctuation indices. Minimum concentrations (Cmin) and maximum plasma concentrations (Cmax) of the compound of the invention may be kept in a small range. To measure the fluctuation between Cmin and Cmax the the compound of the invention levels are measured at the steady state and the fluctuation index is calculated: (Cmax – Cmin)/Cav wherein Cmax is the maximum concentration, Cmin is the minimum concentration, Cavs is the average concentration observed in a certain time interval e.g 24 hours at steady state.

Low fluctuation of Cmin and Cmax may avoid peak values of the compound of the invention plasma levels, which can be toxic for the patient. Lower fluctuation may provide better tolerablility and safety for the patient treated with a compound of the invention.

The oral dosage forms of the invention may be produced in conventional manner by mixing the components. The resultant mixture may be in powder form which may be pressed to form a tablet in conventional tabletting machines.

Conveniently oral dosage forms of the invention may be produced by compressing a compound of the invention with e.g. conventional tabletting excipients to form a tablet core using conventional tabletting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating. Granulation methods are described, for example, in R. Voigt, Lehrbuch der Pharmazeutischen Technologie, Verlag Chemie, 6th edition, pages 156-169.

Granules may be produced in a manner known per se, for example using wet granulation methods known for the production of "built-up" granules or "broken-down" granules.

Methods for the formation of built-up granules may comprise, for example simultaneously spraying the granulation mass with granulation solution and drying, for example in a drum granulator, in pan granulators, on disc granulators, in a fluidised bed, by spray-drying or spray-solidifying, or operate discontinuously, for example in a fluidised bed, in a batch mixer or in a spray-drying drum.

Depending on the method used, the granulation mass may be in the form of a premix or e.g. may be obtained by mixing a compound of the invention with one or more excipients. The wet granules are preferably dried, for example by tray drying or in a fluidised bed.

Oral dosage forms of the invention may contain, in addition to a compound of the invention and at least one disintegrant, conventional excipients depending on the exact nature of the formulation. Suitable categories of excipients include fillers, lubricants, film coating agents, binders, glidants, solubilizers and surface-active substances.

Excipients disclosed in the literature, as for instance in Fiedler's "Lexikon der Hilfstoffe", 4th Edition, ECV Aulendorf and "Handbook of Pharmaceutical Excipients", Wade and Weller, Third Edition (2000), the contents of which are incorporated herein by reference, may be used in the pharmaceutical compositions according to the invention. Conveniently the excipients comprise less than 40 % of the weight of the dosage form.

We have found that certain excipients exhibit especially interesting properties as retarding agents in oral dosage forms of the invention such as

polymethylacrylates, having a molecular weight of ≥ 100 000 Daltons, for example copolymers of acrylic or methacrylic acid esters, known as Eudragit RL 30D (Handbook of Pharmaceutical Excipients loc.cit., p. 402); and

ethyl cellulose such as Aquacoat available as a 30 wt.% ethylcellulose dispersion from FMC.

Microcrystalline cellulose is preferably present. It may be used as a filler. Examples include the Avicel® type (FMC Corp.), for example of the types AVICEL PH101, 102, 105, RC581 or RC 591 (Fiedler loc.cit., p. 216), Emcocel® type (Mendell Corp.) Elcema® type (Degussa), Filtrak® type, Heweten® type or Pharmacel®. Preferably the weight ratio of microcrystalline cellulose to the compound of the invention is from about 1:8 to about 1:14, more preferably 1:10 to 1:12.

Examples of suitable disintegrants include: (i) natural starches, such as maize starch, potato starch, and the like, directly compressible starches, e.g. Sta-rx® 1500, modified starches, e.g. carboxymethyl starches and sodium starch glycolate, available as Primojel®, Explotab®, Explosol®, and starch derivatives such as amylose; (ii); crosslinked sodium carboxymethylcellulose, available as e.g. Ac-di-sol®, Primellose®, Pharmacel® XL, Explocel®, and Nymcel® ZSX; (iii) alginic acid and sodium alginate; (iv) methacrylic acid-divinylbenzene copolymer salts, e.g. Amberlite® IRP-88, and (v) magnesium aluminium silicate, bentonite, alginic acid and alginates. In a preferred embodiment of the invention, the disintegrant is a natural starch, more preferably maize starch.

Alternatively, polyvinyl-polypyrrolidone can be used as a disintegrant. A preferred example is a crosslinked polyvinylpyrrolidone, e.g. crospovidones, e.g. Polyplasdone® XL (Fiedler loc.cit., p. 1245) and Kollidon® CL disintegrant.

Colloidal silicas e.g. Aerosil 200 (Fiedler, loc.cit., p117) may be preferably present. These may act as a glidant. Examples of other glidants include: silica, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

Magnesium stearate is a preferred excipient. It may function as a lubricant. Examples of other lubricants include: calcium stearate, zinc stearate, talc, polyethylene glycol, stearic

acid, sodium benzoate, sodium dodecyl sulfate, also know as sulphuric acid monododecyl ester sodium salt available as Duponol C (Fiedler loc.cit., p. 517), mineral oil, and polyoxyethylene monostearate. A combination of lubricants may also be used.

An alkyl sulfate may be present. It may function as a surfactant. Preferred examples are sodium dodecyl sulfate (n-tetradecyl sulfate, n-hexadecyl sulfate or n-octadecyl sulfate for example sodium, potassium or magnesium n-dodecyl sulfate. Sodium lauryl sulphate (SDS) for example is available as Duponol C (Fiedler loc.cit., p. 517). If desired non-ionic surfactants may be used of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000 stearate. Examples of other surfactants include: phosphatides such as lecithin, acacia, tragacanth, polyoxyethylated sorbitan monooleate and other ethoxylated fatty acid esters of sorbitan, polyoxyethylated fats, polyoxyethylated oleotriglycerides, linolizated oleotriglycerides, polyethylene oxide condensation products of fatty alcohols, alkylphenols or fatty acids or also 1-methyl-3-(2-hydroxyethyl)imidazolidone-(2). "Polyoxyethylated" means that the substances in question contain polyoxyethylene chains, the degree of polymerization of which generally lies between 2 and 40 and in particular between 10 and 20.

A granulate of a compound of the invention may be coated. Suitable coating materials include those materials conventionally used in coating tablets, granules and the like. In one group of embodiments the coating is water soluble. In another group of embodiments the coating is gastric juice resistant but soluble in intestinal juices.

Unlesss otherwise indicated, all percentages are weight by weight.

Oral dosage forms of the invention may be combined with immediate release systems. A combination may be a double-layer tablet comprising an immediate release system and a matrix system wherein a compound of the invention, e.g. licarbazepine. A double-layer tablet may comprise two doses of a compound of the invention, one part being adapted to provide a sustained release dose and another part adapted to provide an immediate release dose.

For tablets comprising licarbazepine, by immediate release is meant release of at least 90 % of the dose within 0.5 hours and 100% of the dose within 1.5 hours under in vitro licarbazepine test dissolution conditions of the invention.

In one embodiment of the invention, preferably a 500 mg licarbazepine dose is used.

Furthermore, the invention provides

- A disintegrating tablet having modified release granules comprising licarbazepine and at least one polymer as retarding agents adapted to be administered once a day; in particular such disintegrating tablet wherein the at least one polymer is selected from polymethacrylates and ethylcellulose. Such disintegrating tablet preferably has no food effect.

- A pharmaceutical oral controlled release composition comprising licarbazepine displaying a plateau profile between about 4 and 25 hours after administration;

- A method of orally administering licarbazepine for the treatment of affective disorders, said method comprising orally administering to a patient in need of licarbazepine therapy once-a-day an oral dosage form of the invention.

Following is a description by way of example only of compositions and processes of the invention. In Example 1, 500 mg of drug substance is employed. In a similar manner tablets can be prepared comprising 750 mg, 250 mg or 125 mg of drug substance.

<u>Abbreviations</u>

Ac	acetyl
aqu.	aqueous
dansyl	5-(dimethylamino)-1-naphthalenesulfonyl
Et	ethyl
HPLC	high pressure liquid chromatography
Me	methyl
NMR	nuclear magnetic resonance

RT	room temperature
THF	tetrahydrofuran
Ts	tosyl

Example 1: Modified Release Granules Comprising Licarbazepine in a Disintegrating Tablet

Coarse licarbazepine drug substance is spray-granulated in a fluid bed dryer (Aeromatic Fielder MP1) using a dispersion of Eudragit E30D and ethyl cellulose. The granules are then dried and screened using a Frewitt mill equipped with 1 mm mesh. Cellulose crystalline, croscarmellose sodium, maize starch and Aerosil 200 are also screened and added to the granules. The blend is mixed using a bin blender (Turbula). Magnesium stearate is screened through a hand screen (0.8 mm mesh) and added. The final blend is mixed using a bin blender (Turbula).

The final blend is compressed using a Korsch PH250 tabletting press. The tablets are ovaloid, curved, 18 mm long, 7.1 mm wide and without a breaking bar. The weight of the tablet is 790 mg.

Formulation

Tablet components:	(mg)
Licarbazepine	500.00
Eudragit E30D	100.00
Ethyl cellulose aqueous dispersion	35.00
Cellulose microcrystalline	45.00
Croscarmellose Na	40.00
Maize starch STA-RX	62.50
Aerosil 200	3.75
Magnesium stearate	3.75
Tablet weight	**790.00**

Example 2: Procedure for the enantioselective Transfer Hydrogenation of 10-Oxo-10,11-dihydro-dibenzo[*b*,*f*]azepine-5-carboxylic acid amide to *R*(-)-10,11-Dihydro-10-hydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide

To a mixture of 10-oxo-10,11-dihydro-dibenzo[*b*,*f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene, Aldrich, Switzerland) (8.8 mg, 0.0138 mmol) in CH_2Cl_2 (15 ml) is added dropwise a premixed solution of formic acid and NEt_3 (5:2, 328 mg:289 mg) at 23 °C and stirred for 10 min. The clear solution is heated to reflux for 16 h. The reaction mixture is cooled to RT, diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *R*(-)-10,11-dihydro-10-hydroxy-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (enantiomeric purity (ee) > 99 % determined by HPLC on Chiracel OD, Retention time: 9.46 min. $[\alpha]_D^{rt}$ = -195.3 ° (ethanol). ^{1}H-NMR (400 MHz, $CDCl_3$):7.70-7.20 (m, 8 H), 5.30 (br s,1 H), 5.10-4.60 (br s, 2 H), 3.75-3.40 (m, 1 H), 3.20-2.90 (m, 1 H), 2.50 (br s, 2 H). NMR-Datas refer to Lit.: Benes, J et al., *J. Med. Chem.* 1999, *42*, 2582-2587. Molecular weight: 254.291

Example 3: Procedure for the enantioselective Transfer Hydrogenation of 10-Oxo-10,11-dihydro-dibenzo[*b*,*f*]azepine-5-carboxylic acid amide to *S*(+)-10,11-Dihydro-10-hydroxy-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide

To a mixture of 10-oxo-10,11-dihydro-dibenzo[*b*,*f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene) (11 mg, 0.0173 mmol) in CH_2Cl_2 (15 ml) is added in two portions a premixed solution of formic acid and NEt_3 (5:2, 656 mg:578 mg) at 23 °C and stirred for 10 min. After that formic acid is added (50 µl) and the clear solution is heated to reflux for 16 h. The reaction mixture is cooled to RT, diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *S*(+)-10,11-dihydro-10-hydroxy-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (ee > 99 % by HPLC on Chiracel OD). Retention time: 12.00 min. $[\alpha]_D^{rt}$ = +196.6 ° (ethanol). ^{1}H-NMR (400 MHz, $CDCl_3$):7.70-7.20 (m, 8 H), 5.30 (br s,1 H), 5.10-4.60 (br s, 2 H), 3.75-3.40 (m, 1 H), 3.20-

2.90 (m, 1 H), 2.50 (br s, 2 H). NMR-Datas refer to Lit.: Benes, J et al., *J. Med. Chem.* 1999, *42*, 2582-2587. Molecular weight: 254.291

Alternative production: To a mixture of 10-oxo-10,11-dihydro-dibenzo[*b,f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*S,2S*)-*p*-dansyl-$NCH(C_6H_5)CH(C_6H_5)NH_2](\eta^6$-*p*-cymene) (8.5 mg, 0.012 mmol) in CH_2Cl_2 (15 ml) is added dropwise a premixed solution of formic acid and NEt_3 (5:2, 328 mg:289 mg) at 23 °C and stirred for 10 min. The clear solution is heated to reflux for 16 h. The reaction mixture is cooled to RT, diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *S*(+)-10,11-dihydro-10-hydroxy-5*H*-dibenzo[*b,f*]azepine-5-carboxamide.

<u>Example 4</u>: Preparation of RuCl[(1*S,2S*)-*p*-dansyl$NCH(C_6H_5)CH(C_6H_5)NH_2](\eta^6$-*p*-cymene)

a) Preparation of (S,S)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide: To a solution of (*S,S*)-diphenylethylenediamine (250 mg, 1.2 mmol) and triethylamine (0.5 ml) in THF is added dropwise a solution of dansyl chloride (318 mg, 1.2 mmol) in THF (2 ml) at 0°C. After stirring 16 h at RT the solvent is removed in vacuum and the residue is resolved in methylenchloride (20 ml). The organic solution is washed with $NaHCO_3$ solution (5 ml), dried over Na_2SO_4 and after filtration the solvent is removed. Flash chromatographie afford (*S,S*)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide as yellow oil which crystallizes by drying in vacuum. M: 445.59. ^1H-NMR (400 MHz, $CDCl_3$):8.36 (t, *J* = 7.5 Hz, 2 H), 8.17 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.47 (dd, *J* = 8.8 Hz, 1 H), 7.34 (dd, *J* = 8.5 Hz, 1 H), 7.24-7.16 (m, 4 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 6.99-6.74 (m, 6 H), 4.61 (d, *J* = 8.5 Hz, 1 H), 4.20 (d, *J* = 8.5 Hz, 1 H), 2.80 (s, 6 H).

b) Preparation of RuCl[(1S,2S)-p-dansyl$NCH(C_6H_5)CH(C_6H_5)NH_2](\eta^6$-p-cymene): A solution of (*S,S*)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide (80mg, 0.18 mmol), NEt_3 (36 mg, 0.36 mmol) and $[RuCl_2$(p-cymene)$]_2$ (55 mg, 0.09mmol) in 2-propanol is heated at 80°C for 1 h. The solvent is removed after that und the dark red residue is washed with water (2 ml). The solid is dried in vacuum and used without any purification. M: 715.34.

Claims

1. A pharmaceutical oral controlled release composition comprising 10-hydroxy-10,11-dihydrocarbamazepine.

2. The pharmaceutical composition according to claim 1 being a disintegrating tablet with modified release granules comprising 10-hydroxy-10,11-dihydrocarbamazepine.

3. The pharmaceutical composition according to claim 2 wherein the 10-hydroxy-10,11-dihydrocarbamazepine is present in the granules in a ratio of 60 to 90 % by weight of the modified release granules.

4. A pharmaceutical composition according to claim 2 or 3 wherein the modified release granules comprise as retarding agent at least one polymer selected from polymethacrylates and ethylcellulose.

5. The pharmaceutical composition according to claim 4 comprising polymethacrylates and ethylcellulose wherein the polymethacrylate is present in the granules in a ratio of 5 to 25 % by weight of the modified release granules.

6. A pharmaceutical composition according to claim 4 or 5 comprising polymethacrylates and ethylcellulose wherein the ethylcellulose is present in the granules in a ratio of 2 to 10 % by weight of the modified release granules.

7. A pharmaceutical composition according to any one of claims 1 to 6 comprising from 50 to 80 % by weight of 10-hydroxy-10,11-dihydrocarbamazepine of the total composition.

8. A pharmaceutical composition according to any one of claims 1 to 7 comprising microcristalline cellulose.

9. A pharmaceutical composition according to any one of claims 1 to 8 comprising at least one natural starch as disintegrant.

10. The pharmaceutical composition according to claim 9 comprising maize starch as disintegrant.

11. A pharmaceutical oral controlled release composition comprising 10-hydroxy-10,11-dihydrocarbamazepine wherein in use 70 to 90% of said 10-hydroxy-10,11-dihydrocarbamazepine is released in artificial stomach juices within 6 hours indicated in standard in vitro dissolution tests at 37 degrees Celsius in water using sodium dodecyl sulphate as a solubilizing agent at a concentration of 1% for a 500 mg dosage form.

12. The pharmaceutical oral controlled release composition comprising 10-hydroxy-10,11-dihydrocarbamazepine according to claim 11 wherein in use 75 to 85% of said 10-hydroxy-10,11-dihydrocarbamazepine is released in artificial stomach juices within 6 hours.

13. A pharmaceutical oral controlled release composition according to any one of claims 1 to 12 having no food effect.

14. A disintegrating tablet having modified release granules comprising 10-hydroxy-10,11-dihydrocarbamazepine and at least one polymer as retarding agents adapted to be administered once a day.

15. The disintegrating tablet according to claim 14 wherein the at least one polymer is selected from polymethacrylates and ethylcellulose.

16. A disintegrating tablet according to claim 14 or 15 having no food effect.

17. A pharmaceutical oral controlled release composition comprising 10-hydroxy-10,11-dihydrocarbamazepine displaying a plateau profile between about 4 and 25 hours after administration.

18. Use of 10-hyroxy-10,11-dihydrocarbamazepine and excipients as defined in any one of claims 1 to 17 for the preparation of a medicament for the treatment of patients with affective disorders.

19. A method of orally administering 10-hydroxy-10,11-dihydrocarbamazepine for the treatment of affective disorders, said method comprising orally administering to a patient in need of 10-hydroxy-10,11-dihydrocarbamazepine therapy once-a-day a pharmaceutical composition according to any one of claims 1 to 17.